REMARKS

The present invention is directed to new dosage forms of atorvastatin that solve the degradation problems associated with atorvastatin formulations of the prior art. In order to advance the prosecution of the application, claim 1 was cancelled and replaced with new claim 43. New claims 43 specifies that the formulation must contain less than 5 w/w% of an alkalizing agent. Support for this amendment may be found on page 13 of the specification at lines 17-19. Further claim 43 specifies the formulation must contain at least 40 w/w % of a diluent. Support for these amendments made be found on page 11, at line 12. The reasons for these amendmets are discussed below in addressing the rejctions under 35 USC 103.

Non-elected claims 8, 9 and 18-42 were cancelled. It is respectfully submitted the claims are in condition for allowance. Reconsideration is respectfully requested.

REJECTIONS

A) Double Patenting

Claims 1-7 and 10-17 were provisionally rejected for obviousness-type double patenting in view of United States Patent application Numbers 10/828,079 and 10/828,419. It is respectfully submitted that this rejection is moot in view of the attached terminal disclaimer.

B) 35 USC 112

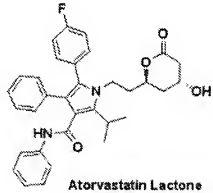
Claim 3 was rejected under the first paragraph of 35 USC 112. The basis of this rejection is Example 2 that exemplifies the preparation of an atorvastatin formulation using a "wet granulation". This formulation was not stable since approximately one quarter of the atorvastatin was converted to the lactone.

This example is a comparative example and was included to show the advantages of the invention. The formulations prepared in Example 3 using dry granulation did not exhibit such elevated levels of lactone conversion which is discussed further below. If the USPTO wishes, the specification can be amended to label Example 2 as "Comparative Experiment".

C) 35 USC 103

The claims were rejected under 35 USC as being obvious in view of Kerc et al when combined with either Nagaprasad et al or Fox et al. It is respectfully submitted that the rejection should be withdrawn for the following reasons.

Kerc et al, Nagaprasad et al, Fox et al, and Applicants all address a common problem, namely the chemical instability associated with statins. As is discussed on page 13 of the specification, atorvastatin is subject to chemical degradation when stored under ambient conditions. Atorvastatin is converted to atorvastatin lactone as shown below.



Atorvastatin Lactone

The prior art teaches that this problem can be solved by incorporating basic substances into the formulation, thus preventing degradation of the atorvastatin (see United States Patent No. 5,686,104). The primary reference, Kerc et al, also uses pH to both minimize degradation of atorvastatin and to improve its solubility. The USPTO's attention is directed to pages 3, 4, and 5 of Kerc et al where he describes his invention. For example, at page 3, lines 29-33, Kerc et al states the object of the invention relates to "a pharmaceutical formulation containing an alkalizing or buffering substance". On page 5, beginning at line 28, Kerc et al describes the pH adjusting substances that may be incorporated into his formulations.

Likewise, all of the formulations exemplified in Kerc et al incorporate substantial quantities of a base, except for the three comparative formulations shown in Tables 1 and

4 of Kerc et al. Formulations A2, AK3, and AA3 did not contain a base. Kerc et al's description of these formulations show that he considered them inferior and not part of his invention, due to the limited solubility he reports for these formulations. Kerc et al was using these formulations as comparators to illustrate his invention.

All of the remaining examples from Kerc et al use substantial quantities of base. In Example 1, on page 14, Kerc et al uses magnesium oxide to stabilize the formulation. It was present in the quantity of 10.4 w/w%. In Example 2, sodium phosphate is the base and is present in the quantity of 45 w/w%. Similar results are depicted in Examples 3-6 on page 15 of Kerc et al. Thus to one of ordinary skill in the art, Kerc et al teaches that atorvastatin formulations must contain substantial quantities of bases in order to both prevent the degradation and to enhance solubility.

By contrast, Applicants have found an alternative solution to the degradation problem typically associated with atorvastatin formulations. Instead of relying on pH, Applicants have discovered that the granulation process can impact atorvastatin stability. More specifically, Applicants have discovered that utilization of a dry granulation process will minimize the formation of atorvastatin lactone, even if the base is omitted from the formulation.

The USPTO's attention is directed to Examples 2 and 3 appearing on pages 16-18 of Applicants specification. As mentioned above, Example 2 shows the preparation of an atorvastatin formulation using a wet granulation process. The formulation contained microcrystalline cellulose, lactose, croscarmellose and hydroxypropyl cellulose. It did not contain a base to stabilize the atorvastain. The materials were stored at elevated temperatures and humidity for a month. Approximately 25 % of the atorvastatin was converted to the lactone.

In Example 3, an identical formulation was prepared using a dry granulation. This formulation was also stored at elevated temperatures and humidity for a month. The atorvastain lactone content was only 0.17%.

Claim 43 has been drafted to differentiate the invention from Kerc et al. Claim 43 specifies that the formulation must contain less than 5 w/w % of an alkalizing agent (i.e. a base). As noted above, all of Kerc et al's formulation contained substantial quantities of base (i.e. in excess of 10 w/w %).

This same claim limitation is also relevant to Nagaprasad et al. Nagaprasad et al was focused on stabilizing another structurally distinct statin, pravastatin. Like, Kerc et al, Nagaprasad et al uses pH to minimize formation of the lactone of pravastatin.

Nagaprasad states on page 1, at lines 7 and 8, that the formulation must contain a carrier that imparts a pH of 6.5-8. This same qualification is repeated through out the specification at multiple locations, such as at pages, 4, 5, 8, etc. At page 5, lines 29 and 30, Nagaprasad et al states the composition will preferably contain calcium carbonate. Thus Nagaprasad et al both expressly and implicitly teaches that pravastatin formulations must contain substantial quantities of base.

As the USPTO has noted, on page 4 Nagaprasad states that dry granulation improves the stability of pravastatin. Other than the necessity to maintain a pH of at least 6.5-8, Nagprasad et al does not give any indication any particular excipients must be used in a dry granulation for the statin, pravastatin.

This differs significantly from atorvastatin. The USPTO's attention is directed to page 9 of the specification, for the discussion beginning at line 26. When the inventors attempted to dry granulate atorvastatin they discovered a significant problem. A significant amount of the drug remained unbound to excipients. Such unbound drug will lead to the production of dosage forms not having a uniform content of drug. This could lead to either under dosing or over dosing of atorvastatin. As noted on page 11, at lines 18-23, the inventors have discovered that atorvastatin will preferentially bind to selected excipients, thus avoiding the under and over dosing problem.

Claim 43 has been amended to reflect the inventors' solution to this problem. Claim 43 specifies that the formulation must contain at least 40 w/w% of at least one, or a combination of, the diluents specified in that claim. These diluents bind atorvastatin and solve the under dosing problem the inventors discovered with dry granulations of atorvastatin. Nagaprasad gives no guidance that dry granulations of atorvastatin would have such a problem, or how one could solve them.

The comments above regarding Nagprasad et al are equally applicable to Fox et al. Fox et al was attempting to minimize the formation of the lactones of both pravastatin and atorvastatin. Fox et al teaches that it is important to maintain the pH above 6.5 and points to a series of amide stabilizers that will accomplish this.

Fox et al gives no suggestion that dry granulation will solve the instability associated with atorvastatin. Further, Fox et al gives no suggestion of the problems associated with dry blending atorvastatin described above. Further Fox gives no guidance on how to solve that problem.

In summary, the claims have been amended to differentiate them from Kerc et al, Napaprasad et al and Fox et al. The claims now specify that the formulation must contain less than 5 w/w % of an alkalizing agent. Claim 46 speices the formulation must have less than 3 w/w% and claims 47 specifies it must have less than 2.

Unlike the prior art, Applicants do not use pH to minimize lactone formation. Applicants have discovered that lactone formation may be minimized by dry granulation. Further applicants have discovered that dry granulation creates another problem, the potential of improper dosing, and have found a solution to this problem as well. Claim 43 has been amended to reflect this contribution to the art. Claim 43 specifies the excipients that should be used and the relative amount of these components that should be incorporated into the formulation.

Reconsideration is respectfully requested.

Respectfully submitted,

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